Metabolic dysfunction-associated steatotic liver disease in people living with HIV: a framework for integrated screening and care

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Metabolic dysfunction-associated steatotic liver disease (MASLD) has emerged as a major cause of liver-related and cardiometabolic morbidity and mortality among people living with HIV, driven by ageing, obesity, type 2 diabetes, and long-term antiretroviral therapy. Approximately 20–41% of people living with HIV have MASLD, and significant liver fibrosis affects 12–20% of all people living with HIV, suggesting a fibrosis burden that exceeds that of the general population. HIV-specific mechanisms, including chronic immune activation, altered adipose distribution, and historical exposure to older antiretroviral agents, contribute to a more severe metabolic liver phenotype. Sex, gender, and social determinants of health—including menopause, food insecurity, and material deprivation—further influence fibrosis risk and access to care. International guidelines now recommend routine fibrosis screening in at-risk people living with HIV with the use of non-invasive tools such as transient elastography and serum biomarkers. Lifestyle interventions, optimisation of metabolic comorbidities, and emerging therapies including glucagon-like peptide-1 receptor agonists are reshaping management. Inclusion of people living with HIV in MASLD therapeutic trials remains a major, unmet research priority.

Introduction

Globally, about 40 million people are living with HIV, and approximately 1·3 million new acquisitions continue to occur annually.[1] As antiretroviral therapy (ART) has led to improved survival, multimorbidity management has become a defining feature of contemporary HIV care. Historically, hepatitis C (HCV) and hepatitis B virus (HBV) coinfections were major drivers of cirrhosis, hepatic decompensation, and hepatocellular carcinoma in people living with HIV. However, widespread access to curative medications for HCV and treatment of chronic HBV have substantially reduced the burden of viral hepatitis-related liver disease.[2] Despite these advances, liver-related morbidity and mortality remain an important concern among ageing people living with HIV.[2,3] Indeed, metabolic dysfunction-associated steatotic liver disease (MASLD) has emerged as a leading cause of chronic liver disease in people living with HIV and hepatic steatosis and progressive fibrosis are now recognised as major contributors to adverse liver and extrahepatic outcomes in the contemporary ART era.[4] The adoption of the umbrella term steatotic liver disease (SLD) in 2023, encompassing MASLD, its inflammatory phenotype metabolic dysfunction-associated steatohepatitis (MASH), and alcohol-related liver disease, among others, is particularly relevant to people living with HIV.[5] Unlike the previous non-alcoholic fatty liver disease (NAFLD) definition, the SLD framework allows coexisting metabolic, viral, inflammatory, and alcohol-related contributors to be captured within a single diagnostic construct, a major advantage in people living with HIV where mixed causes are common.[5,6] Beyond traditional metabolic risk factors, additional drivers of steatosis and fibrosis progression include chronic immune activation, long-term ART exposure, and social determinants.[6–8] The convergence of these factors creates a uniquely complex liver disease phenotype.[9] With the availability of large multinational cohorts, advanced imaging modalities, and emerging MASH therapies, the field is now positioned to redefine the epidemiology, pathogenesis, diagnosis, and management of MASLD in HIV with unprecedented clarity. In this Review, we summarise current evidence and propose a comprehensive framework for the screening and management of MASLD in people living with HIV.

Epidemiology and burden of MASLD in people living with HIV

The prevalence of MASLD among people living with HIV matches or exceeds that observed in the general population.[10–13] Early studies reported substantial heterogeneity owing to differences in diagnostic methods, study populations, and inclusion criteria, but more recent meta-analyses provide increasingly robust estimates. A 2023 meta-analysis of 43 studies including 8230 people living with HIV reported a pooled NAFLD prevalence of 33·9% (95% CI 29·7–38·4%).[4] A subsequent 2025 meta-analysis using updated SLD nomenclature reported an overall prevalence of 39% (33–44%) across 58 studies.[14] Prevalence was highest in high-income regions, reaching 41% and particularly affecting North America and Europe, where metabolic comorbidities and long-term ART exposure are common. By contrast, lower estimates of 20% have been reported in lower-middle-income countries, although insufficient diagnostic access likely contributes to under-recognition. Across cohorts, MASLD remains the dominant SLD phenotype, accounting for 75% of cases, whereas metabolic dysfunction-associated alcohol-related liver disease comprises a smaller yet clinically relevant subgroup (19% of cases).[11]

Several studies suggest that MASLD in people living with HIV is associated with greater liver disease severity

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than among people without HIV.[15,16] Overall, histological studies consistently demonstrate a substantial burden of MASH and fibrosis across diverse populations of people living with HIV, despite differences in study design, inclusion criteria, and indications for liver biopsy (table 1).[15–24] Prevalence estimates of MASH vary from 8% in consecutively screened populations to more than 50% in studies enriched for elevated aminotransferases. Meta-analysis showed a pooled estimate of 24% (95% CI 17–30%).[14] Across imaging-based cohorts, 12–20% of people living with HIV exhibit clinically significant fibrosis (F2–F4), whereas 6–10% have advanced fibrosis (F3–F4).[10,11,13,15,16,25] These estimates derive from studies including heterogeneous populations, ranging from individuals with confirmed MASLD, to broader people living with HIV cohorts undergoing fibrosis assessment irrespective of steatosis status or liver disease aetiology. Nevertheless, estimates are consistent across regions and indicate a fibrosis burden exceeding that observed in the general population. Factors associated with liver fibrosis include older age, metabolic comorbidities, longer HIV duration, lower nadir CD4 cell count, persistent immune activation, and historical exposure to thymidine analogue nucleoside reverse transcriptase inhibitors (NRTIs).[10,11,13,15,16,25] Emerging histological data suggest that people living with HIV might exhibit a distinct liver injury phenotype characterised by greater fibrosis despite less hepatocellular ballooning than in people without HIV, supporting the possibility of HIV-specific pathogenic mechanisms.[15] Although longitudinal data remain scarce, available studies indicate meaningful rates of fibrosis progression, driven largely by metabolic dysfunction, chronic inflammation, and ageing, even in the absence of viral hepatitis co-infection (table 2).[10,26–32] Reported incidence rates of new-onset significant liver fibrosis range from 0·9 to 2·8 per 100 person-years, whereas progression from early fibrosis to clinically significant fibrosis or from clinically significant fibrosis to cirrhosis has been reported at rates as high as 12·7 per 100 person-years.[10,26,29] Importantly, data from 2024 suggest that fibrosis regression can occur in people living with HIV, particularly among individuals who achieve weight loss, improve metabolic risk factors, or receive effective interventions targeting steatosis and metabolic dysfunction.[29] These findings highlight the dynamic nature of MASLD and the potential reversibility of liver injury. Emerging data also suggest an incidence of liver-related events at 8·6 per 1000 person-years, including decompensation, hepatocellular carcinoma, and liver-related mortality.[31] People living with HIV with MASLD might experience rates of fibrosis progression and liver-related complications at least similar to those observed in the general MASLD population, with HIV-specific factors potentially amplifying risk in some individuals. Advanced fibrosis and cirrhosis remain the principal determinants

	Study design and country	Number of participants	Age, years	Male sex, %	Race or ethnicity, %	Alcohol excess, %	BMI, kg/m²	Diabetes, %	HIV infection duration, years	Elevated ALT, %	MASH, %	F2–F4 fibrosis, %
Ingiliz et al, 2009[18]	Prospective; France	30	NA	97%	NA	0	23·0 (SD 3·1)	NA	13 (IQR 9–15)	100%	53·3%	20%
Crum-Cianflone et al, 2010[22]	Prospective; USA	55 with histology (of 216)	41 (IQR 30–46)	96·2%	White (47·7%); Black (27·3%)	12·5	26·0 (SD 4·1)	5·1%	14 (IQR 6–20)	100%	7·3%	3·6%
Sterling et al, 2013[23]	Prospective; USA	14	45 (SD 10)	71%	White (57%)	0	29·9 (SD 7·4)	0	NA	100%	28·6%	35·7%
Morse et al, 2015[17]	Prospective; USA	62	50 (range 17–67)	94%	White (65·0%); Black (8·0%)	0	27·6 (range 15·3–47·1)	9·7%	17·5 (range 2·3–27·8)	100%	54·8%	19·4%
Vodkin et al, 2015[16]	Prospective; USA	33	44·8 (SD 9·4)	78·8%	Hispanic ethnicity (51·5%)	0	29·8 (SD 6·0)	18·2%	NA	NA	63·6%	33·3%
Benmassaoud et al, 2018[21]	Prospective; Canada	17 with histology (out of 202)	53·9 (SD 8·3)	78·3%	White (45·2%); Black (37·6%)	0	27·7 (SD 4·5)	7%	19·9 (SD 7·4)	75%	11·4%	15·3% (58·9% in participants with MASH)
Iogna Prat et al, 2019[20]	Retrospective; UK	97	47 (SD 10)	93%	White (66%); Black (30%)	20	27 (SD 6)	11%	10·5 (SD 9·3)	100%	8·2%	20%
Maurice et al, 2021[19]	Retrospective; international	116	48·4 (SD 10·9)	93·2%	White (77·1%); Black (11·0%)	0	29·2 (SD 5·5)	21·1%	13·0 (IQR 7–21)	100%	49·1%	57·7%
Busca et al, 2022[24]	Prospective; Spain	65	49·3 (IQR 44·0–53·4)	92·3%	White (88·3%); Black (3·3%)	0	28·9 (IQR 25·5–30·8)	66%	14·3 (IQR 7·4–20·6)	100%	61·0%	29·2% (F1-F2)
Allende et al, 2024[15]	Retrospective; USA	107	48·9 (SD 9)	79·4%	White (64·5%); Black (13·1%)	0	30·6 (SD 5·8)	24·3%	13·7 (SD 8)	92·5%	36·0%	67·3%

Continuous variables are expressed as mean and SD or median (IQR or range) and categorical variables are presented as percentages. Significant liver fibrosis is defined as stage F2–F4 on a scale from 0 to 4. Alcohol excess was defined as daily consumption more than 30 g per day for men and more than 20 g per day for women and as more than 140 g per week for men and more than 70 g per week for women. ALT=alanine aminotransferase. MASH=metabolic dysfunction-associated steatohepatitis. MASLD=metabolic-dysfunction-associated steatotic liver disease. NA=not available.

Table 1: **Histological studies of MASLD in people living with HIV**

	Study design; country	Study population	Number of participants	Age, years	Male sex, %	HIV infection duration, years	Diagnostic method	Follow-up duration	Hepatic steatosis or fibrosis incidence or progression
Riviero-Juarez et al,2013[32]	Prospective; Spain	People living with HIV undergoing prospective LSM monitoring irrespective of steatosis status	210	44·3 (SD 9·7)	66·1%	8·89 (SD 5·3)	LSM >7·2	18 months (IQR 12–26)	Fibrosis incidence 10·9%
Sebastiani et al, 2015[26]	Retrospective; Canada	People living with HIV followed for incident steatosis and fibrosis	796	43·5 (IQR 36–49·7)	84%	6·3 (IQR 1·7–13·3)	Hepatic steatosis index >36; FIB-4 >3·25	4·9 years (IQR 2·2–6·4)	Steatosis incidence 6·9 per 100 PY; fibrosis incidence 0·9 per 100 PY
Pembroke et al, 2017[10]	Prospective; Canada	People living with HIV undergoing longitudinal assessment of hepatic steatosis and fibrosis	313	50 (IQR 43–54)	76·7%	15 (IQR 8–22)	CAP >248 or transition >292; and LSM >7·1 or >12·5	15·4 months (IQR 8·5–23·0)	Steatosis progression 37·8 per 100 PY; fibrosis progression 12·7 per 100 PY
Lallukka-Brück et al, 2019[27]	Retrospective–prospective; Finland	People living with HIV with and without ART-associated lipodystrophy followed for steatosis progression	42	41·9 (SD 1·3)	82·9%	23·5 (SD 0·7)	^{1}H-MRS, Liver fat fraction >5·56%; LSM by transient elastography >8·7 or LSM by MRE >3·62	15·7 years (range 12·3–16·4)	Steatosis prevalence baseline 35%, end of follow-up 32%; fibrosis prevalence 9·52%
Iacob et al, 2022[28]	Retrospective; Romania	People living with HIV followed for fibrosis progression irrespective of steatosis status	111	35 (IQR 26–45)	51·4%	12 (IQR 6–15)	APRI >0·5 or FIB-4 >1·45	60 months	Fibrosis APRI baseline 5·4%, end of follow-up 8·1%; FIB-4 baseline 7·2%, end of follow-up 9%
Guaraldi et al, 2024[29]	Retrospective; international	People living with HIV evaluated for the effect of MASLD and weight gain on fibrosis progression	1183	52·9 (IQR 46·3–58·2)	77·5%	18 (IQR 9–26·9)	LSM >8 or >13	2·5 years (IQR 1·9–3·5)	Fibrosis incidence 2·8 per 100 PY
Fittipaldi et al, 2025[30]	Prospective; Brazil	People living with HIV without baseline fibrosis followed for incident fibrosis according to baseline MASLD status	304	44 (IQR 36–52)	43·4%	9·6 (IQR 5·3–15·7)	LSM >8	7·4 years (6–8·3)	Fibrosis incidence 17·3 per 1000 PY

Continuous variables are expressed as mean plus SD, or median (IQR or range). Categorical variables are presented as percentages. Significant liver fibrosis is defined as stage F2–F4 on a scale from 0 to 4. Fibrosis incidence is defined as development of F2–F4 in patients with F0 or F1 at baseline. Fibrosis progression is defined as development of F2–F4 in patients with F0 or F1 at baseline or development of cirrhosis (F4) in patients with F2 or F3 at baseline. APRI=aspartate aminotransferase-to-platelet ratio index. ART=antiretroviral therapy. CAP=controlled attenuation parameter. FIB-4=fibrosis-4 index. LSM=liver stiffness measurement. MASLD=metabolic dysfunction-associated steatotic liver disease. MRE=magnetic resonance elastography. MRS=magnetic resonance spectroscopy. PY=person-years.

Table 2: **Longitudinal progression of hepatic steatosis and liver fibrosis in people living with HIV mono-infection**

of adverse hepatic outcomes, including hepatocellular carcinoma and liver transplantation. In people living with HIV without viral hepatitis, the reported incidence of hepatocellular carcinoma remains relatively low (0·08 per 1000 person-years), although MASLD-specific data are not available.[33] Contemporary data on liver transplantation attributable specifically to MASLD in people living with HIV remain scarce; however, non-viral liver disease has emerged as the leading indication for liver transplantation among people living with HIV in the USA.[34] Because not all studies specifically evaluated MASLD-related fibrosis, these estimates should be interpreted as reflecting the broader burden of liver fibrosis in people living with HIV rather than fibrosis attributable exclusively to MASLD.

Beyond liver-related complications, MASLD is increasingly recognised as a multisystem disorder associated with cardiovascular disease, type 2 diabetes, chronic kidney disease, extrahepatic malignancies, and impaired quality of life.[35] In people living with HIV, the coexistence of chronic immune activation, inflammation, and cardiometabolic dysfunction can further amplify both hepatic and extrahepatic morbidity. Longitudinal studies have shown that MASLD predicts development of metabolic comorbidities among people living with HIV alone.[36] In a large cohort of veterans, individuals with both HIV and MASLD experienced higher rates of adverse liver and cardiovascular outcomes than individuals with MASLD alone.[37] The relationship between MASLD and cardiovascular disease might also differ according to body composition, with lean people (BMI <25 kg/m²) living with HIV exhibiting distinct metabolic perturbations associated with incident cardiovascular disease.[38] MASLD and liver fibrosis have also been linked to frailty and poorer quality of life in people living with HIV.[39,40] Emerging evidence further suggests a potential link between MASLD and cognitive impairment through pathways involving systemic inflammation, metabolic dysfunction, and the gut–liver axis in people living with HIV.[41] Together, these findings underscore the importance of integrated cardiometabolic risk stratification and multidisciplinary care in people living with HIV with MASLD.

Multifactorial pathogenesis of MASLD in HIV

The pathogenesis of MASLD in people living with HIV reflects the convergence of amplified metabolic drivers, HIV-specific factors, ART exposure, and syndemic social and gender-related determinants (figure 1). Compared with populations without HIV, these pathways accumulate earlier and more frequently in people living with HIV. Insulin resistance remains the key driver of MASLD. Type 2 diabetes, obesity, dyslipidaemia, and hypertension strongly predict hepatic steatosis, inflammation, and fibrosis progression and are highly prevalent in people living with HIV.[2,42] Downstream mechanisms of MASLD, including mitochondrial dysfunction, excess lipid oxidation, and generation of reactive oxygen species, promote hepatocellular injury, release of inflammatory cytokines (ie, interleukin-6 and cytokeratin-18 [CK-18]), and stellate-cell activation.[6] People living with HIV exhibit elevated inflammatory and oxidative stress markers, partly reflecting persistent immune activation and legacy mitochondrial toxicity from historical ART exposures.[2,6] Genetic susceptibility also contributes to disease severity. The patatin-like phospholipase domain-containing protein 3 (PNPLA3) I148M variant remains a key determinant of MASLD severity, although associations in people living with HIV are inconsistent and might interact with inflammatory pathways and social determinants of health.[24] A study of 764 people living with HIV reported an association of PNPLA3 risk allele and SLD in lean individuals.[43] Adipose tissue dysfunction further contributes to lipotoxicity and inflammation in people living with HIV.[6] Gut dysbiosis represents another important pathway: HIV is associated with reduced microbial diversity and altered gut permeability, promoting persistent microbial translocation and systemic inflammation, even with suppressive ART.[44] Emerging data suggest that HIV-associated dysbiosis correlates with MASLD severity.[45]

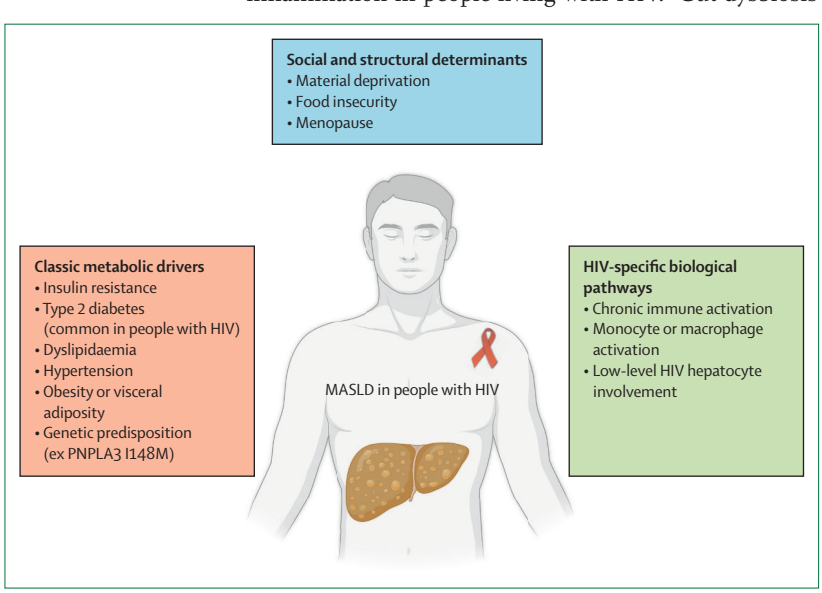

Figure 1: **Conceptual framework of MASLD multifactorial pathogenesis in people living with HIV**
Classic metabolic risk factors interact with HIV-specific biological mechanisms, including chronic immune activation, monocyte or macrophage activation, and low-level HIV persistence. These pathways are further modified by social, structural, and commercial determinants of health, ultimately promoting steatosis, inflammation, and fibrosis. MASLD=metabolic dysfunction-associated steatotic liver disease. PNPLA3 I148M=patatin-like phospholipase domain-containing protein 3 I148M variant.

Beyond metabolic risk, HIV introduces unique biological processes that amplify liver injury, many of which persist despite effective ART and durable viral suppression. Persistent immune activation and gut microbial translocation promote monocyte and macrophage activation, Kupffer-cell stimulation, and profibrotic cytokine production.[6] These pathways are strongly associated with fibrosis, cardiometabolic disease, and mortality in people living with HIV. Although viral suppression likely attenuates some inflammatory and immune-mediated mechanisms involved in steatosis and fibrosis, residual immune activation, adipose tissue dysfunction, and metabolic abnormalities persist despite virological control. Consequently, MASLD remains highly prevalent in contemporary cohorts of people living with HIV, suggesting that viral suppression alone does not prevent steatosis or progressive liver disease. HIV RNA and DNA have been detected in hepatocytes and non-parenchymal cells, and HIV might directly impair mitochondrial function and sensitise the liver to metabolic injury.[6] HIV-associated gut barrier disruption further perpetuates portal inflammation and fibrogenesis. HIV-associated lipodystrophy can also contribute to MASLD pathogenesis. Although lipoatrophy is largely a legacy effect of older NRTIs, central fat accumulation and visceral adiposity remain prevalent in the contemporary ART era, compounded by rising obesity rates among people living with HIV. Visceral adiposity, peripheral lipoatrophy, and profound insulin resistance directly promote MASLD and highlight the long-lasting metabolic consequences of earlier HIV therapies.[6] Older NRTIs (ie, zidovudine, stavudine, and didanosine) caused mitochondrial toxicity, impaired β-oxidation, microvesicular steatosis, and peripheral lipoatrophy. Early protease inhibitors promoted dyslipidaemia, insulin resistance, and direct hepatocyte stress.[6,46] These effects are not believed to be fully reversible and might contribute to chronic hepatic vulnerability in ageing people living with HIV. Contemporary ART regimens have a more favourable hepatic safety profile; however, metabolic concerns persist. Integrase strand transfer inhibitors (INSTIs), particularly dolutegravir and bictegravir, have been associated with excessive weight gain in some people, particularly women of African ancestry.[47,48] Whether INSTIs directly promote steatosis or steatosis occurs secondary to ART-associated weight gain remains debated. Although in 2021, Bischoff and colleagues reported a possible association between INSTI exposure and steatosis progression,[49] subsequent studies did not

confirm this finding.[11,29,50] A study of 872 women with HIV initiating ART showed increased hepatic steatosis risk only within the first year after INSTI initiation, warranting longer follow-up and evaluation on fibrosis outcomes.[51] An association between use on tenofovir alafenamide and hepatic steatosis has also been suggested,[49] although this requires confirmation. Non-nucleoside reverse transcriptase inhibitors, particularly rilpivirine and doravirine, appear to have comparatively favourable metabolic profiles, although data specifically addressing MASLD outcomes remain scarce.[2] Importantly, interpretation of these associations warrants caution, as most studies are observational and susceptible to confounding by indication, weight gain after treatment initiation, temporal changes in ART prescribing patterns, and coexisting metabolic risk factors. Metabolic consequences of ART can differ according to body composition, with distinct metabolic signatures observed among lean people living with HIV and those with obesity, underscoring the heterogeneity of HIV-associated MASLD[53] and supporting the concept that lean MASLD can represent a unique biological phenotype.[38] These findings also highlight the potential of omics-based approaches to refine mechanistic understanding and risk stratification in HIV-associated MASLD.

Syndemic social adversity further amplifies biological risk in people living with HIV. Canadian data showed striking levels of material (45%) and social (72%) deprivation, particularly among women, racialised individuals, and those with type 2 diabetes. Moreover, material deprivation was associated with liver fibrosis and adverse liver outcomes.[7] In a US cohort, food insecurity affected 31% of people living with HIV and was associated with advanced liver fibrosis among those with type 2 diabetes.[8] Structural inequities, including housing instability, stigma, and insufficient access to nutritious food, might influence dietary quality and nutritional status, exacerbating metabolic dysfunction and impeding lifestyle-based interventions, emphasising the need for culturally and socially tailored strategies. The role of diet and nutrition as mediators linking social and structural determinants to MASLD risk and progression remains understudied in people living with HIV. Sex-related biological factors and gendered social determinants further modulate MASLD risk. Women with HIV experience earlier menopause, extending the window of vulnerability for MASLD. Although premenopausal women with HIV have lower MASLD and fibrosis prevalence than men, fibrosis progression accelerates around perimenopause.[53] Oestrogen decline, immune changes, and increased visceral adiposity likely contribute. Moreover, women with HIV disproportionately experience food insecurity, deprivation, and caregiving burden, further amplifying metabolic and inflammatory pathways.[7]

Diagnostic strategies for MASLD in people living with HIV

Liver enzymes perform poorly as screening tools because many individuals with MASLD, including nearly half of individuals with MASH and 20% of those with advanced fibrosis, can present with normal aminotransferase levels.[54] Consequently, clinically significant liver disease can remain undetected in people living with HIV. Because fibrosis stage, rather than steatosis alone, is the strongest predictor of liver-related and all-cause mortality, early identification and risk stratification are essential.[31,42] Liver biopsy remains the diagnostic gold standard but is impractical for routine HIV care and population-level screening.[9,42] Consequently, non-invasive diagnostic tools have become central to MASLD evaluation and fibrosis staging. Serum-based biomarkers, such as AST-to-platelet ratio index and the fibrosis-4 (FIB-4) index, are widely used in people living with HIV because of their simplicity and accessibility, with reported area under the curve (AUC) of 0·61–0·86 and 0·64–0·81, respectively, against liver biopsy.[19,55,56] However, in a multinational study of 4917 people living with HIV undergoing transient elastography-based screening, FIB-4 showed only modest accuracy for clinically significant fibrosis (AUC 0·69) and misclassified 36% of individuals with clinically significant fibrosis as low risk.[57] Performance of the FIB-4 index was poorer in MASLD than non-MASLD, mirroring observations in populations with obesity or type 2 diabetes.[58] Incorporating cardiometabolic and HIV-specific variables improved fibrosis discrimination, supporting screening frameworks that integrate traditional metabolic and HIV-related risk factors, particularly in individuals with discordant metabolic and liver phenotypes or indeterminate non-invasive test results. Nevertheless, current guidelines continue to recommend FIB-4 as a pragmatic first-line tool within MASLD screening pathways.[9] Transient elastography with controlled attenuation parameter (CAP) is a validated modality for the assessment of both fibrosis and steatosis in people living with HIV. Studies comparing liver stiffness measurement by transient elastography with liver biopsy demonstrated good diagnostic performance for clinically significant fibrosis with the use of a threshold of 7·1 kPa, with sensitivity ranging from 80% to 93%, and AUC values between 0·61 and 0·93.[17,55,56] CAP performs well for steatosis detection, with an AUC of 0·87 against liver histology and an optimal threshold of 280 dB/m.[55] Magnetic resonance proton density fat fraction and magnetic resonance elastography offer higher diagnostic accuracy, but remain limited by cost and availability, restricting their use primarily to inconclusive cases, research, or tertiary-care settings.[59] Screening strategies should integrate metabolic risk factors with HIV-specific determinants. These factors are not routinely incorporated into current MASLD screening pathways, yet emerging evidence suggests they might improve identification of people living with

HIV at highest risk of clinically significant fibrosis.[57] Additional risk-modifying factors, including material and social deprivation, food insecurity, and earlier menopause among women with HIV, might justify earlier or more frequent screening.[7,8,53] Particular attention should be paid to lean people living with HIV, as approximately a quarter of MASLD cases occur in people without obesity.[60,38,52] Reliance on obesity alone as a screening trigger might therefore miss a substantial proportion of at-risk individuals, highlighting the need for risk stratification strategies that extend beyond BMI. The 2025 European AIDS Clinical Society (EACS) guidelines recommend a multistep, non-invasive pathway beginning with FIB-4 followed by transient elastography for secondary risk assessment.[9] Individuals with low-risk FIB-4 values should undergo periodic reassessment, whereas people with elevated scores or transient elastography values should be referred for specialist evaluation. EACS also acknowledges that second-line non-invasive tools (ie, transient elastography, enhanced liver fibrosis test, and shear-wave elastography) might not be universally available and therefore supports direct hepatology referral when appropriate (figure 2). Transient elastography and platelet count additionally guide decisions regarding endoscopic screening for oesophageal varices according to Baveno criteria, which have proven safe and effective in people living with HIV.[10,61] Following diagnosis, MASLD surveillance should be integrated into HIV care pathways to promote both liver health and healthy ageing. Individuals with low fibrosis risk require periodic reassessment, whereas people with clinically significant fibrosis warrant closer monitoring for disease progression and liver-related complications. Because fibrosis risk evolves with ageing, metabolic health, weight gain, menopause, and ART modifications, repeated risk stratification is preferable to a one-time assessment and should be accompanied by ongoing management of cardiometabolic comorbidities and lifestyle factors. Embedding this framework within routine HIV care will facilitate earlier identification of individuals at high risk, reduce diagnostic delays, and improve access to emerging therapies.

A metabolic health framework for MASLD management in people living with HIV

Principles of integrated care

MASLD is increasingly recognised as one of the most clinically consequential manifestations of metabolic dysfunction in people living with HIV. Accordingly, a metabolic health framework encompassing metabolic risk factors, body composition changes, lifestyle determinants, and long-term outcomes across the care continuum provides a useful foundation for integrated, patient-centred care.[47] As people living with HIV age, it offers a practical framework for addressing the combined effects of chronic HIV, ART exposure, ageing, sex-related and gender-related factors, and social determinants of health.[47] Because these factors evolve over the life course, metabolic health can serve as a longitudinal roadmap to guide clinical priorities during key transitions, including ART initiation and modification, and age-related changes in adiposity and muscle mass.[29,47] Beyond viral

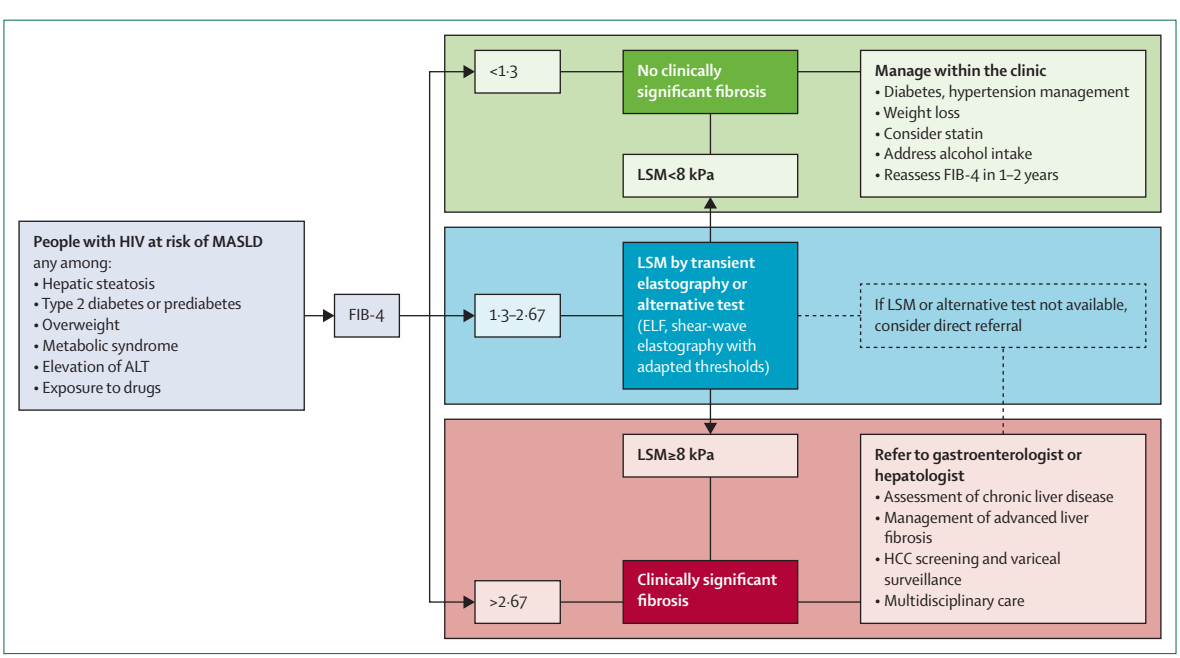

***Figure 2*: Proposed screening and risk stratification pathway for MASLD-related liver fibrosis in people living with HIV**
The pathway integrates metabolic risk factors and HIV-specific determinants, using sequential non-invasive assessment to identify individuals with clinically significant fibrosis who might benefit from specialist evaluation and closer monitoring. ALT=alanine aminotransferase. ELF=enhanced liver fibrosis test. FIB-4=fibrosis-4 index. HCC=hepatocellular carcinoma. LSM=liver stiffness measurement. MASLD=metabolic dysfunction-associated steatotic liver disease.

suppression, therapeutic goals include preserving physical function, preventing comorbidities, and promoting healthy ageing.[47,62] Patient engagement and shared decision making are central to this model.[47] Clinicians can empower patients by strengthening health literacy, clarifying individualised risk profiles, and co-developing realistic goals for nutrition, physical activity, and self-management. Comprehensive metabolic health can be targeted through lifestyle interventions, structured exercise, nutritional counselling, ART optimisation, and pharmacological therapies such as statins, sodium-glucose co-transporter 2 (SGLT2) inhibitors, and glucagon-like peptide-1 (GLP-1) receptor agonists. Within this framework, systematic assessment of hepatic steatosis and fibrosis should be integrated into routine HIV care alongside management of metabolic risk factors. This approach should also incorporate preventive liver health measures, including assessment of hepatitis A virus and HBV immunity and vaccination of susceptible individuals, consistent with current EACS recommendations.[9] The following section outlines therapeutic approaches aimed at preventing liver disease progression while restoring long-term metabolic health.

Lifestyle changes

Lifestyle modification remains the cornerstone of MASLD therapy across populations, including people living with HIV.[9] Because BMI is the most commonly reported predictor of MASLD in people living with HIV, individualised interventions targeting caloric reduction, improved diet quality, alcohol reduction, and increased physical activity are key to management.[4] In the general population, a 500–1000 kcal per day energy deficit and a weight loss target of 7–10% yield meaningful improvements, with more than 7% weight loss leading to MASH resolution and more than 10% associated with fibrosis regression.[42] Similar targets are presumed beneficial for people living with HIV, although high-quality evidence is scarce. In 2025, the first randomised controlled trial of lifestyle intervention in people living with HIV with MASLD was conducted. Over 12 months, a dietitian-led programme integrating caloric reduction, aerobic training, and progressive resistance exercise resulted in 27·9% MASLD resolution, significantly outperforming standard care (9·8%; p=0·034).[63] Aerobic training reduced hepatic fat content, whereas resistance training preserved or increased muscle mass, an important advantage in people living with HIV, who are at increased risk of sarcopenia. These findings confirm that structured lifestyle intervention is both feasible and effective within HIV care settings. A Mediterranean-style diet is associated with reduced liver fat and improved metabolic health in people with MASLD, and is recommended by EACS guidelines.[9,42] In patients undergoing weight loss, structured nutritional care should prioritise adequate protein intake (>1·0 g/kg per day, and 1·2–1·5 g/kg per day during active weight loss), micronutrient monitoring, and combined aerobic and resistance exercise to preserve lean mass and reduce the risk of sarcopenic obesity.[42] Because no safe alcohol threshold has been established for MASLD, individuals should be advised to minimise alcohol consumption and avoid it completely in the presence of clinically significant fibrosis or cirrhosis. Avoidance of fructose-rich beverages and limiting processed red meat consumption are also consistently recommended.[42,64] Counselling should also address recreational substance use, as some substances can contribute to hepatotoxicity and compound existing liver injury.

ART-related interventions

In the context of HIV, ART represents an additional modifiable determinant of liver and metabolic health. The goal is two-fold: maintain durable viral suppression while minimising metabolic toxicity or excessive weight gain. Early evidence suggested that ART switches could modulate hepatic fat. Maraviroc was associated with reduced hepatic steatosis in a feasibility trial; however, a subsequent trial did not confirm these findings.[65] Switching from efavirenz to raltegravir reduced hepatic steatosis in 39 people with HIV and HCV co-infection; however, no effect on steatosis was observed when the switch was conducted in 31 people living with HIV alone.[51,66] More recent concerns have focused on weight gain associated with INSTIs, particularly dolutegravir and bictegravir.[47,48] Although any weight gain can increase MASLD risk, causal links with INSTIs remain debated, and recent studies[29,50,51] in people living with HIV have not consistently demonstrated direct effects of INSTIs on liver fat or fibrosis progression. Some non-nucleoside reverse transcriptase inhibitors might offer a more favourable metabolic profile, but have not been studied specifically in the context of MASLD.[9] To date, no specific ART regimen is recommended solely for people living with HIV and MASLD, but awareness of metabolic effects remains key within a comprehensive care framework. According to EACS guidelines, in people living with HIV at risk for or living with MASLD, ART regimens with minimal metabolic effect should be prioritised.[9]

Pharmacological therapy

Pharmacological options for MASLD have expanded substantially in the general population, with two landmark approvals for non-cirrhotic MASH with clinically significant fibrosis (F2–F3): resmetirom (US Food and Drug Administration [FDA] 2024; European Union 2025) and semaglutide (US FDA 2025; European Union 2026).[67,68] In the MAESTRO-NASH trial, resmetirom, an oral thyroid hormone receptor-β selective agonist, significantly improved both coprimary histological endpoints at week 52, with MASH resolution achieved in 25·9–29·9% of treated participants compared with 9·7% receiving placebo and fibrosis

improvement in 24·2–25·9% versus 14·2%, respectively.[67] Similarly, in the ESSENCE trial, once-weekly semaglutide 2·4 mg achieved MASH resolution in 62·9% of participants compared with 34·3% receiving placebo, whereas fibrosis improvement occurred in 36·8% versus 22·4%.[68] These studies establish the therapeutic relevance of targeting both fibrosis and metabolic dysfunction. However, the applicability of these results to people living with HIV remains uncertain because this population was excluded from the development programmes. Evidence for MASLD-specific pharmacotherapies in people living with HIV remains insufficient. Vitamin E, previously recommended for MASH in selected individuals without type 2 diabetes,[69] improved aminotransferases, CAP, and CK-18 concentrations in a small open-label study of people living with HIV, although fibrosis did not improve.[70] Pioglitazone has demonstrated reductions in hepatic fat and lobular inflammation in pilot studies in people living with HIV, but evidence for MASH resolution remains limited.[69,71] Among therapies studied specifically in people living with HIV, tesamorelin, a synthetic growth hormone-releasing hormone analogue approved for HIV-associated lipodystrophy, reduced intrahepatic triglyceride content by 32% and achieved steatosis resolution in 35% of participants compared with 4% receiving placebo.[72] Fibrosis progression occurred in only 10·5% of treated participants versus 37·5% in the placebo group, suggesting a potential antifibrotic effect. Semaglutide has shown promising results in people living with HIV. In the SLIM LIVER open-label study of 49 people living with HIV, 58% reached at least 30% reduction in intrahepatic triglycerides and 29% achieved complete MASLD resolution over 24 weeks.[73] Significant reductions in bodyweight, waist circumference, and glycaemic indices were observed. However, rapid weight loss associated with GLP-1 receptor agonists can be accompanied by lean mass loss. In SLIM LIVER,[74] psoas muscle volume decreased by 9·3%, although functional measures remained preserved. These findings support combining GLP-1 receptor agonists with resistance training, particularly in people living with HIV, who are already at increased risk of sarcopenia. In randomised studies, semaglutide reduced markers of systemic inflammation and monocyte activation in people living with HIV including high-sensitivity C-reactive protein, interleukin-6, and soluble CD163.[75] Improvements in lipidomic profiles and DNA-methylation–based ageing indices have also been reported.[76] Together, these findings suggest that GLP-1 receptor agonists can address multiple pathways relevant to HIV-associated metabolic dysfunction beyond weight reduction alone. Although dedicated randomised trials with liver-related outcomes remain needed, these observations support a potentially important role for incretin-based therapies in people living with HIV with MASLD, obesity, type 2 diabetes, or clinically significant fibrosis. However, access remains a major challenge. Unlike ART, GLP-1 receptor agonists and dual glucose-dependent insulinotropic polypeptide and GLP-1 receptor agonists are not consistently available. Disparities in prescribing have already been documented in the USA, with Black people living with HIV less likely to receive semaglutide than White individuals despite a similar metabolic indication.[77] Equitable access to emerging therapies will be essential to avoid widening disparities in care. Beyond GLP-1 receptor agonists, SGLT2 inhibitors and metformin improve glycaemic control, reduce visceral adiposity, and exert favourable cardiometabolic effects.[78] Although MASLD-specific data in people living with HIV remain scarce, these agents are widely used in people living with HIV and type 2 diabetes because of their established safety, cardiorenal benefits, and potential to reduce hepatic fat. Optimisation of other cardiometabolic comorbidities remains equally important. Hypertension and dyslipidaemia are highly prevalent among people living with HIV and contribute substantially to cardiovascular risk, a leading cause of morbidity and mortality in individuals with MASLD. Management should therefore include guideline-directed blood pressure control and lipid-lowering therapy, with treatment targets individualised according to overall cardiovascular disease risk. Statins, the key treatment for dyslipidaemia, deserve special consideration. Although statins are not MASH-directed therapies, they remain a cornerstone of cardiovascular disease risk reduction in people living with HIV with

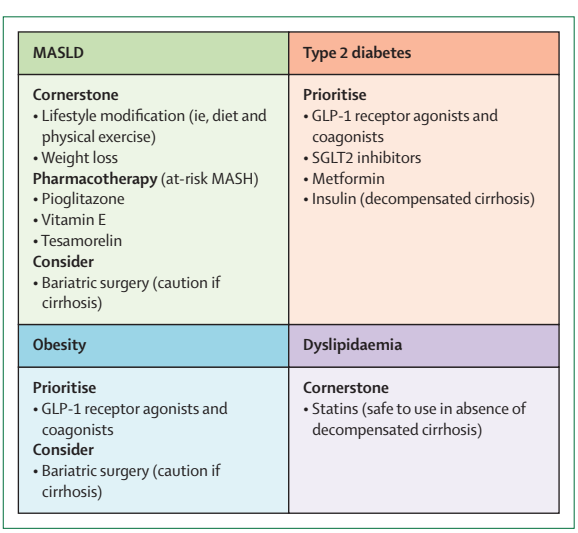

Figure 3: **Integrated management framework for MASLD in people living with HIV**
Lifestyle interventions are the cornerstone of care for all patients, whereas metabolic optimisation and MASH-directed therapies are tailored according to fibrosis severity and risk of progression. Regular reassessment is recommended because fibrosis risk is dynamic and influenced by metabolic, HIV-related, and social determinants. MASH=metabolic dysfunction-associated steatohepatitis. MASLD=metabolic dysfunction-associated steatotic liver disease. GLP-1=glucagon-like peptide-1. SGLT2=sodium-glucose co-transporter 2.

MASLD. In the REPRIEVE trial, pitavastatin reduced major adverse cardiovascular events by 35% among people living with HIV at low-to-moderate traditional cardiovascular disease risk, supporting statin therapy as a foundational component of cardiometabolic management.[79] Statins are also considered safe in MASLD and compensated advanced chronic liver disease, although evidence for direct liver-related benefits remains insufficient.[9]

Bariatric surgery

Bariatric surgery is effective for weight loss and can lead to substantial improvement in metabolic comorbidities and liver fibrosis. Data increasingly support its safety and efficacy in people living with HIV, if ART absorption and drug–nutrient interactions are carefully managed postoperatively. In people living with HIV with obesity and MASLD, metabolic bariatric surgery can improve long-term metabolic outcomes and is indicated, according to current guidelines, in individuals with BMI of at least 40 kg/m² or BMI of less than 40 kg/m² with uncontrolled obesity-related organ dysfunction.[9]

Overall, effective management of MASLD in people living with HIV requires an integrated, holistic approach encompassing hepatic and metabolic health, cardiovascular disease risk reduction, healthy ageing, and people-centred care (figure 3).[9,80] Since 2024, approvals of resmetirom and semaglutide have transformed the therapeutic landscape for MASH with fibrosis and expanded opportunities for individualised care. Combining lifestyle interventions, optimisation of cardiometabolic comorbidities, ART optimisation, and emerging MASH-directed therapies offers the potential to improve both liver-related and overall health outcomes in people living with HIV.

Future directions

MASLD has emerged as a major and clinically consequential comorbidity in people living with HIV, driven by the convergence of metabolic dysfunction, HIV-related and ART-related exposures, and social determinants of health. Although steatosis is common, fibrosis remains the principal determinant of adverse hepatic outcomes and should remain the focus of screening and management. Systematic screening with validated non-invasive tools, integrated within routine HIV care, represents the most pragmatic strategy for early identification and risk stratification. Despite therapeutic advances since 2024, important knowledge gaps remain (panel).[81] People living with HIV have been systematically excluded from most pivotal MASH therapeutic trials despite a substantial burden of fibrosis and cardiometabolic disease.[78,81] Future priorities include intentional inclusion of people living with HIV in clinical trials, development and validation of HIV-specific diagnostic and risk stratification tools, routine incorporation of sex-disaggregated and gender-disaggregated analyses, and implementation science approaches to support patient-centred models of care. Finally, scalable strategies leveraging digital health, task-shifting, precision hepatology, and social determinants of health will be essential to modernising MASLD care and ensuring equitable access to emerging therapies. Together, these advances offer a roadmap towards more effective and inclusive management of MASLD in people living with HIV and hold the potential to meaningfully improve long-term health outcomes for this high-risk population.

***Panel*: Key unmet needs in research and clinical care for MASLD in people living with HIV**

Disease burden and outcomes

Epidemiology

Contemporary estimates of metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic dysfunction-associated steatohepatitis (MASH), fibrosis, and liver-related outcomes across diverse HIV populations, including women, older adults, and populations from low-income and middle-income countries

Natural history

Longitudinal studies evaluating fibrosis progression, cirrhosis, hepatocellular carcinoma, liver-related mortality, and extrahepatic outcomes in the contemporary antiretroviral therapy (ART) era

Healthy ageing

Understanding interactions between MASLD, frailty, sarcopenia, cardiovascular disease, cognitive decline, and ageing in people living with HIV

Mechanisms and risk stratification

HIV-specific mechanisms

Better understanding of the roles of persistent immune activation, mitochondrial dysfunction, gut–liver axis alterations, microbial translocation, adipose tissue dysfunction, body composition changes, and long-term ART exposure in MASLD pathogenesis

Diagnostics and risk stratification

Validation of non-invasive tests, biomarkers, and fibrosis prediction models specifically in people living with HIV; development of HIV-specific biomarkers and risk stratification tools; and integration of HIV-specific determinants into screening pathways

Therapeutic innovation

Therapeutics

Inclusion of people living with HIV in pivotal MASH clinical trials; dedicated studies evaluating the efficacy and safety of resmetirom, glucagon-like peptide-1 receptor agonists, dual or triple agonists, and emerging therapies

ART optimisation

Clarification of the long-term hepatic and metabolic effects of contemporary ART regimens and strategies to minimise metabolic toxicity while maintaining viral suppression

Implementation and equity

Implementation science

Development and evaluation of integrated screening, referral, and follow-up pathways embedded within routine **HIV care**

Health equity

Addressing disparities related to sex, race and ethnicity, socioeconomic deprivation, food insecurity, and access to diagnostics and therapies

Search strategy and selection criteria

References for this Review were identified through searches of PubMed from Jan 1, 2000, to May 1, 2026, using combinations of the terms "HIV", "people living with HIV", "metabolic dysfunction-associated steatotic liver disease", "MASLD", "steatotic liver disease", "metabolic dysfunction-associated steatohepatitis", "MASH", "non-alcoholic fatty liver disease", "NAFLD", "nonalcoholic steatohepatitis", "NASH", "liver fibrosis", "transient elastography", and "FIB-4". Additional articles were identified through the authors' personal files and by reviewing reference lists of relevant publications. Only articles published in English were considered. We also included relevant clinical practice guidelines, consensus statements, and landmark studies considered important to the scope of this Review. References were selected based on relevance, originality, methodological quality, and clinical significance.

Contributors

GS contributed to the study concept and design, acquisition and interpretation of data, drafting of the manuscript, and critical revision of the manuscript. THL, AC, FC, JEL, JVL, JKR, and GG contributed to the study concept, interpretation of data, and critical revision of the manuscript. All the authors declare they have participated in the preparation of the manuscript and have seen and approved the final version.

Declaration of interests

GS has acted as speaker for Merck, Gilead, AbbVie, Eli Lilly, Novo Nordisk, Lupin, Boehringer Ingelheim, and Biron; served as an advisory board member for GlaxoSmithKline, Gilead, Echosens, and Novo Nordisk; received unrestricted grants from Novo Nordisk; and she is the President of the Canadian Association for the Study of the Liver. AC has served as a speaker for GSK, MSD, Gilead Sciences, and Eva Pharma; and participated in advisory boards for GSK, MSD, Gilead Sciences, and Eva Pharma, all outside the submitted work; received research support to institution from Eva Pharma and Roche. JEL receives research support from Gilead Sciences and Madrigal Pharmaceuticals; and has provided consulting services to ViiV Healthcare, all outside of the submitted work. JVL received research grants to his institutions from Boehringer Ingelheim, Echosens, Gilead Sciences, Madrigal Pharmaceuticals, MSD, Novo Nordisk, and Pfizer, consulting fees from Echosens, GSK, Madrigal Pharmaceuticals, Novo Nordisk, Pfizer, Sonic Incytes, and Takeda; and honoraria for lectures from Echosens, Gilead Sciences, GSK, and Novo Nordisk, outside of the submitted work. JKR has received honoraria for consulting or speaking at educational events from Abbott, AbbVie, Boehringer Ingelheim, MSD, Gilead, Janssen, and ViiV. GG received a research grant and speaker honoraria from Gilead, ViiV, Merck, and Janssen and attended advisory boards of Gilead, ViiV, and Merck. THL and FC declare no competing interests.

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